FOURTH GRANSTEIN DECLARATION

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Docket No.: 02650/100F966-US2
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Richard D. Granstein

Confirmation No. 8709

Application No.: 09/679,776

Art Unit: 1632

Filed: October 5, 2000

Examiner: Q. Li

For: PROTECTIVE IMMUNITY OR IMMUNOLOGICAL TOLERANCE INDUCED WITH RNA, PARTICULARLY TOTAL CELLULAR RNA

DECLARATION OF RICHARD D. GRANSTEIN UNDER 37 C.F.R. § 1.132

MS AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, Richard D. Granstein, declare that:

1. I am a citizen of the United States and reside in Greenburgh, New York.

2. I received a M.D. from the University of California School of Medicine in 1978.

3. I am currently the Chairman of Dermatology at Weill Medical College of Cornell University, New York (the Assignee of the above-identified U.S. Patent

Application) where I have been employed since 1995. I specialize in dermatology and am particularly interested in immunologic disorders of the skin.

4. I am the named inventor of the above-identified U.S. Patent Application.

5. I understand that the Examiner now takes the view that only transplant tissue antigen RNA derived from the grafted tissue themselves would be effective to induce tolerance to grafted tissue, as opposed to cells taken from other sources which also contain transplant tissue RNA.

6. A central tenet of transplantation biology is that the risks of allograft rejection are related to mismatching of classical *major histocompatibility complex* (MHC) class I and MHC class II molecules (1,2). The term MHC class I and MHC class II antigens are subsets of, and encompassed by the term "transplant antigen" as used in the specification. This is believed to result from recognition of these molecules as foreign by recipient T cells via two different mechanisms. In direct allorecognition, recipient T cells recognize foreign peptide-MHC complexes on donor cells (1). In the indirect mechanism, recipient T cells recognize foreign peptides from graft cells presented by self-MHC molecules of recipient dendritic cells (1). Even with potent immunosuppressive agents, it is the state of the art to match MHC molecules to the greatest extent possible to avoid transplant rejection.

7. Our technology involves a novel mechanism of inducing tolerance to antigens, including alloantigens, by administration of RNA coding for these antigens

intravenously. In my opinion, RNA from any tissue which includes RNA (or total messenger RNA) that expresses classical MHC class I and MHC class II molecules and that is syngeneic or isologous to the graft would be capable of inducing tolerance to the graft. There is nothing inherent to graft tissue cells that would dictate that only RNA sourced from these cells induces tolerance to the transplant graft tissue.

8. Indeed, in the experiment presented, we utilized total cellular RNA from spleen lymphoid cells to induce tolerance to skin allografts. Thus, it is my opinion that any tissue expressing MHC class I and MHC class II molecules is suitable for preparation of RNA for inducing tolerance to allogenic transplantation. In practical terms, in humans it would be desirable to prepare RNA from circulating lymphoid cells in the blood as these are easily obtained. RNA can be amplified if sufficient amounts cannot be obtained directly from the cells harvested.

I further declare that statements made in this Declaration are of my own knowledge and are true and that all statements made on information and belief are believed to be true and further these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: 1/27/05

Richard D. Granstein